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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Improvements in or relating to Injectable Thyroxine Preparations

I MURRAY ISRAEL, a citizen of the United States of America, of 265 Locust Lane, East Hills, Roslyn Heights, New York, United States of America, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to injectable pharmaceutical compositions for the parenteral therapeutic use of thyroxine.

Compositions according to the present invention have broad utility in human and veterinary medicine and are particularly useful in the treatment of hypercholesterolemia and related metabolic imbalances as well as the hyperventilation that accompanies such conditions.

However, the parenteral use of thyroxine in humans as a therapeutic agent for prolonged administration has not proven satisfactory. As a matter of fact, it is impossible to continue parenteral administration in this manner, since this substance, when administered alone, induces symptoms attributable to the malfunctioning of the temperature-regulating system of the body and of the autonomic nervous system, whereby the administration of thyroxine in large doses or in frequently repeated normal doses, in most human subjects, or even in relatively infrequent usual doses in occasional human subjects, causes palpitation, extreme nervousness and tremulousness and an increase in body heat production.

It has now been discovered that thyroxine is rendered therapeutically acceptable for parenteral administration even when large doses are administered or when usual doses are given in rapid sequence, if in association with thyroxine there is parenterally administered at least a certain quantity of macromolecular substance of a certain electrical charge, and calcium gluconate. The calcium gluconate, in the presence of the other ingredients, gives a prolonged relief from hyperventilation.

The macromolecular substances of the present invention are therapeutically acceptable electronegative colloids in aqueous dispersion. They are of very high molecular weight, at least about 100,000, and are properly referred to briefly as macroanions. Upon solution or dispersion in a menstruum or solvent, macroanions exhibit an electronegative charge due to the ionization of functional acidic groups which they contain. Thus, heparin is a macroanion because of the dissociation of sulfamido and sulfate groups in its molecular structure, while carboxymethylcellulose is a macroanion because it is a massive, colloidally dispersable molecule which in aqueous dispersion yields an electronegative charge because of ionization of its carboxyl groups. The same is true of other macroanions because of the presence in the molecule of other acidic or potentially acidic groups such as nitrite, nitro, sulfone, free tertiary phosphate or imino groups.

The macroanion of the present invention consists of purified or crystalline vitamin B_{12} and gelatin, with the gelatin present in a greater quantity than the vitamin B_{12}.

It is believed that the stoichiometric mixture for purposes of forming this aggregate is equimolar, that is, fifteen parts by weight of gelatin to one part by weight of vitamin B_{12}. However, as the vitamin B_{12} is considerably more expensive than the gelatin, and as the gelatin is innocuous in any event, it is preferred to provide an excess of gelatin over that theoretically required, in order to assure complete utilization of the vitamin B_{12}. Therefore, the preferred weight ratio of gelatin to vitamin B_{12} is twenty to one.

Thyroxine is the most active ingredient of the pharmaceutical composition of the present invention, and its minimum effective

[*Price 5s. 0d.*]

quantity per dose, according to the present invention, is about 0.3 mg. Its preferred dosage is 0.5 mg. As to thyrotoxicity, no upper limit is imposed on the quantity of thyroxine by thyrotoxicity, as the macroanion is effective to cover all therapeutically acceptable doses; however, limits on the quantity of thyroxine are imposed by considerations other than thyrotoxic effects.

The quantity of macroanion and the quantity of thyroxine must be related to each other so that the macroanion is present in much greater quantity than the thyroxine. Specifically, the macroanion must not be present in amounts less than about five times the weight of the thyroxine. Preferably, it is present in quantities at least ten times the amount of the thyroxine, and the particularly preferred concentration ratio is twenty to one.

The quantity of calcium gluconate and the quantity of thyroxine should also be related to each other. There should be at least twenty times as much gluconate as thyroxine present, preferably at least about fifty times as much, more preferably at least about one hundred times as much. In terms of absolute quantity, each unit dose should include at least 20 mg. of calcium gluconate, more preferably at least 50 mg. The preferred dosage is around 100 mg; but more may be administered, up to, say, 1000 mg. The increase from 100 mg. up to 1000 mg. seems to produce little if any additional desirable result, on the one hand, but seems on the other hand to be harmless.

Around limitation on the proportions is imposed by the quantity of liquid that may be administered parenterally in a single dosage form. The minimum from a standpoint of the quantity of liquid is 0.1 ml., for less than this cannot accurately be measured in clinical procedures; while the maximum is 5 ml., for obvious reasons. The preferred dosage is 1—2 ml. Thus, considering the maximum volume of liquid to be 5 ml. and the minimum quantity of thyroxine to be 0.3 mg., it will be realized that the medium must contain at least about 0.06 mg./ml. of thyroxine and at least about 0.3 mg./ml. of macroanion. The maximum quantity of macroanion is conditioned only by the concentration at which the aqueous medium tends to form a gel. By the same token, the minimum quantity of macroanion per dose is 1.5 mg. Thus, for the preferred vitamin B_{12}-gelatin aggregate, the minimum vitamin B_{12} is about 0.1 mg., for a maximum ratio of thyroxine to vitamin B_{12} of three to one. But this extreme is not the preferred proportion. Instead, for the vitamin B_{12}-gelatin system, the preferred ratio of thyroxine to vitamin B_{12} is one to one, and a particularly desirable single dosage form consists essentially of 0.5 mg. of vitamin B_{12}, 0.5 mg. of sodium thyroxine, 10 mg. of gelatin, and 100 mg. of calcium gluconate, in 1—2 ml. of physiological saline (0.9% aqueous solution of sodium chloride). It is intended that these liquid dosage quantities be segregated in sealed ampoules such that one ampoule is substantially consumed for each parenteral administration. Of course, for initial dosages, it is well to start at fractions of a normal dose until the dosage regimen is established.

The media in which these materials are contained are aqueous, that is, at least about 50% water. Suitable media are water, physiological saline, solutions of glycols, for example up to about 50% polyethyleneglycol, and various ethanol-water mixtures. They may vary in pH between weakly acidic and strongly alkaline. Above about pH 11, the strong alkalinity renders the injectant injurious to the tissues or to the blood stream into which they are introduced. Below about pH 6, the macroanions precipitate protein in acid medium, except the phthalocyanines which are stabilized sulfonic acid derivatives. The preferred pH range is neutral to 10, preferably nearer the bottom of the range than the top. Hence, another advantage of the vitamin B_{12}-gelatin macroanion is that pH's between 6 and 9 are easily maintained despite the presence of the strongly alkaline thyroxine salts.

EXAMPLE.

One hundred millilitres of a sterile 1% aqueous solution of gelatin is produced by autoclaving an aqueous dispersion of 1 gram of parenteral grade of gelatin in that quantity of water. Fifty milligrams each of crystalline vitamin B_{12} and sodium d-l-thyroxine and ten grams of calcium gluconate are added with stirring. The temperature remains at room temperature and the pH remains at 7 throughout, and the mixture is vigorously agitated to effect solution. After sterilization by filtration, it is sealed in amber ampoules and may be administered parenterally in 1 ml. doses. Prolonged therapy may be conduced with this composition with no evidence of thyrotoxicity.

It has been found that the repeated parenteral administration of the composition of the above example is effective in maintaining human blood cholesterol levels at lower and narrower ranges for long periods of time without relapse.

WHAT I CLAIM IS:—

1. An injectable pharmaceutical composition comprising thyroxine, the composition being therapeutically acceptable for use in a protracted dosage regimen under which its thyroxine content would provoke toxic manifestations if administered alone, consisting essentially of an aqueous medium containing vitamin B_{12}, gelatin and not less than 0.06 mg./ml. of a water-soluble salt of thyroxine, the gelatin being present in an amount

greater than the vitamin B_{12} and the vitamin B_{12} and gelatin together constituting at least five times the weight of the thyroxine, the vitamin B_{12} and gelatin being associated with one another in the form of a macroanionic substance and having a molecular weight of at least 100,000, the composition also containing calcium gluconate in an amount at least twenty times the weight of the thyroxine.

2. A pharmaceutical composition, according to claim 1 in unit dosage form, comprising not more than 5 ml. of an aqueous medium containing not less than 0.3 mg. of the water-soluble salt of thyroxine, the vitamin B_{12} and gelatin together constituting at least five times the weight of the thyroxine and the calcium gluconate being present in an amount of at least 20 mg.

3. A sealed ampoule containing about 1—2 ml. of an aqueous injectable medium containing about 0.5 mg. thyroxine, about 0.5 mg. vitamin B_{12}, about 10 mg. gelatin, and about 100 mg. calcium gluconate, the vitamin B_{12} and gelatin being associated with each other in the form if a macroanionic substance and having a molecular weight of at least 100,000.

4. An injectable pharmaceutical composition according to claim 1, substantially as hereinbefore described.

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